

**REMARKS****The Pending Claims:**

Claims 1-6, 11-14, 16-20, 25-35, 38 and 74-79 are pending in the application. Claims 16-20, 25-35, and 38 are withdrawn from consideration. No claims are currently amended.

The claims are directed to a cell encoded with a semiconductor nanocrystal localized in the cytoplasm, nucleus or an organelle, wherein the cell further comprises an organic fluorophore.

**The Office Action:**

Claims 1-6, 11-14 and 74-79 are rejected.

Claims 1-6, 11-14, 74 and 75 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Millard et al. (U.S. Patent No. 5,534,416) in view of Bawendi et al. (U.S. Patent No. 6,306,610).

Claim 76 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Millard in view of Bawendi as applied to claim 1, and further in view of Rothbard and Sodroski et al. (U.S. Patent No. 6,761,902).

Claim 77 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Millard in view of Bawendi as applied to claim 1, and further in view of Rothbard (U.S. Patent No. 6,306,993).

Claim 78 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Millard in view of Bawendi as applied to claim 1, and further in view of Frankel et al. (U.S. Patent No. 5,652,152).

Claim 79 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Millard in view of Bawendi as applied to claim 1, and further in view of Barbera-Guillem (U.S. Patent No. 6,194,213).

Rejection under 35 U.S.C. § 103(a):

I. Claims 1-6, 11-14, 74 and 75 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Millard et al. (U.S. Patent No. 5,534,416) in view of Bawendi et al. (U.S. Patent No. 6,306,610). In view of the following, Applicants respectfully traverse this rejection.

According to the Office Action, "Millard teaches a cell encoded with two different fluorescent dyes... Bawendi teaches a composition comprising semiconductor nanocrystals associated with cells... The composition [in Bawendi] is associated with cell membranes... Bawendi also teaches nanocrystals coupled to antibodies to target a cellular component. It would have been obvious to one of ordinary skills in the art to replace one of the fluorescent dyes in Millard with semiconductor nanocrystals of Bawendi..." Page 3. Applicants respectfully disagree.

a. *The Restriction Requirement asserted that dye and nanocrystal labeled cells are patentably distinct:*

Applicants respectfully point out that the originally filed method claims were restricted from the present claims as being drawn to a distinct invention because, according to the Examiner, "the method of distinguishably identifying a cell can be performed using another product [i.e. not a nanocrystal] such as magnetic particles or a dye to label the cells." Accordingly, dye labeled cells were determined to be patentably distinct (i.e. non-obvious) from nanocrystal labeled cells. Such a finding is axiomatic to restriction practice (as outlined in M.P.E.P. 804.01).

Accordingly, the proposition that "[i]t would have been obvious to one of ordinary skills in the art to replace one of the fluorescent dyes in Millard with semiconductor nanocrystals of Bawendi" (page 3 of the current Office Action) is contradictory to the initial finding that a nanocrystal labeled cell was not obvious in view of a dye labeled cell.

b. *Nanocrystals are not obvious replacements for the dyes in Millard:*

Nanocrystals exhibit poor solubility, high rigidity, core hydrophobicity, large particle diameter and high ionic density that can adversely affect incorporation, mobility and subsequent viability of live cells. This is contrasted with small molecule dyes, which are small, dynamic, generally hydrophilic, and have limited ionic charges allowing them to passively enter, move and not affect viability of live cells. Millard is directed to the detection of cell viability (i.e. detection of dead and live cells) in a sample. Accordingly, it is unlikely that one would be motivated to replace a large, bulky, ionic sphere of semiconductor material as described in Bawendi, with the easily transported inert dyes described in Millard. Therefore (as already acknowledged by the Examiner in the restriction requirement) nanocrystals are not an obvious replacement for dyes, such as those described in Millard.

Since the restriction requirement acknowledges the non-obviousness of dye labeled cells over nanocrystal labeled cells; Millard effectively teaches away from the present claims; all of the limitations (semiconductor nanocrystals localized in the cytoplasm, nucleus or an organelle) of the claims are not present in the cited art; and neither reference describes nor suggests that a hybrid of a nanocrystal and a dye to encode a cell would be desirable or even plausible, the present obviousness rejection is improper and should be withdrawn.

II. Claim 77 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Millard in view of Bawendi as applied to claim 1, and further in view of Rothbard (U.S. Patent No. 6,306,993). Applicants respectfully traverse this rejection.

According to the Office Action, “[s]ince Millard, Bawendi and Rothbard teach using a label such as nanocrystals and fluorescent dyes for cells or cell membrane, it would have been obvious to one of ordinary skills in the art to associate the polymer composition (comprising a ligand coupled to a transporter) taught by Rothbard to the nanocrystals as a fluorescent label and use in the combined composition taught by Millard and Bawendi because

macromolecules such as peptides and oligonucleotides experience difficulty in passing across the biological membrane and having a polymer as a transportable molecule as that of Rothbard enhances trans-membrane transport." Applicants respectfully disagree.

As described above, Millard and Bawendi do not describe a cell encoded with a semiconductor nanocrystal localized in the cytoplasm, nucleus or an organelle, wherein the cell further comprises an organic fluorophore.

Additionally, semiconductor nanocrystals are large rigid molecules made up of semiconductors such as cadmium selenide and coated with, for example, a zinc sulfide shell, which can additionally be functionalized with charged molecules, such as fatty acids (Bawendi, Column 6, lines 18-50). Rothbard describes the transport of protein and small molecule compositions. Rothbard does not describe the transport of molecules resembling semiconductor nanocrystals. The only reference in Rothbard made to moieties having properties exhibited by semiconductor nanocrystals is in Column 8, lines 15-24: "attaching a large hydrophobic moiety may significantly impede or prevent cross-membrane transport due to adhesion of the hydrophobic moiety to the lipid bilayer." According to Rothbard, large hydrophobic moieties are molecules "such as lipid and fatty acid molecules." The hydrophobic portion of a semiconductor nanocrystal is larger than a fatty acid or lipid molecule.

Furthermore, the nanocrystals described in Bawendi are functionalized with fatty acids (see Figure 4), therefore Rothbard explicitly teaches away from the compositions in Bawendi by stating "the present invention includes conjugates that do not contain large hydrophobic moieties, such as lipid and fatty acid molecules." Rothbard at Column 8 (emphasis added).

Accordingly the obviousness rejection to claim 77 is improper and should be withdrawn.

III. Claim 76 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Millard in view of Bawendi as applied to claim 1, and further in view of Rothbard and Sodroski et al. (U.S. Patent No. 6,761,902). As described above, the

combination of Millard and Bawendi does not render claim 1 obvious. Sodroski does not cure the deficiencies. Therefore, Applicants believe that this rejection has been traversed and should be withdrawn.

IV. Claim 78 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Millard in view of Bawendi as applied to claim 1, and further in view of Frankel et al. (U.S. Patent No. 5,652,152). Applicants respectfully traverse this rejection.

According to the Office Action, “[i]t would have been obvious to one of ordinary skills in the art to use the HIV tat peptide for transporting biological molecules across the cell membrane as taught by Frankel and attach it to a fluorescence semiconductor nanocrystal which associates to a cell membrane or a subcellular organelle so that when biological molecules to be transported reach the cell membrane, they can be transported effectively and efficiently with the aid of the tat peptide and their activity or measurement can be detected by the nanocrystals since the nanocrystals have a spectral emission that is tunable to a desired wavelength, and wherein said wavelength provides information about a biological state or event.” Applicants respectfully disagree.

As described above, Millard and Bawendi do not describe a cell encoded with a semiconductor nanocrystal localized in the cytoplasm, nucleus or an organelle, wherein the cell further comprises an organic fluorophore.

Additionally, similar to Rothbard described above, the “cargo” molecules in Frankel are also biological molecules (i.e. peptides, nucleic acids, oligosaccharides). They inherently possess properties suited for biological systems, including hydrophilicity, flexibility, smaller size (as compared with nanocrystals) and limited ionic charges (as compared with nanocrystals).

On the other hand, nanocrystals, such as those described in Bawendi are large rigid molecules made up of metals such as cadmium selenide and coated with, for example, a zinc sulfide shell, which can additionally be functionalized with charged molecules, such as fatty acids. As with Rothbard, Frankel simply does not provide any motivation or reasonable expectation of success to arrive at

a semiconductor particle complex comprising a semiconductor nanocrystal bound to an HIV tat peptide.

Furthermore, the HIV tat moiety has been shown to be sequestered and inactivated by hydrophobic moieties, such as polystyrenesulfonate (PSS). See U.S. Patent No. 5,308,612. Accordingly, it is unlikely that one would be motivated to use a molecule containing a large hydrophobic moiety, such as a nanocrystal for conjugation to a tat moiety.

Applicants have made it overwhelming clear that the semiconductor nanocrystals of the present invention simply do not conform to procedures described for transport of peptides, nucleic acids, oligosaccharides and the like. It is despite the teachings of Frankel that Applicants performed the experiments to arrive at the present invention showing enhanced delivery of nanocrystals through association with cationic polymers, not because of them.

V. Claim 79 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Millard in view of Bawendi as applied to claim 1, and further in view of Barbera-Guillem (U.S. Patent No. 6,194,213). As described above, the combination of Millard and Bawendi does not render claim 1 obvious. Barbera-Guillem does not cure the deficiencies. Accordingly, Applicants believe that this rejection has been traversed and should be withdrawn.

**CONCLUSION**

In view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent at (541) 335-0165.

Respectfully submitted,

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